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Phenoconversion and Therapeutic Drug Monitoring

Jose de Leon
University of Kentucky, jdeleon@uky.edu

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Jose de Leon, M.D.[1,2]

[1]University of Kentucky Mental Health Research Center, Eastern State Hospital, Lexington, KY, USA

[2]Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, Granada, Spain, and Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apóstol Hospital, University of the Basque Country, Vitoria, Spain.

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Address for correspondence: Jose de Leon, M.D., Room 3A15A, Mental Health Research Center, Eastern State Hospital, 1350 Bull Lea Road, Lexington, KY 40511, USA e-mail: jdeleon@uky.edu. Phone (859) 246-8440 Fax (859) 246-8446.

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I would like to congratulate Shah and Smith for their excellent comprehensive review of phenoconversion [1]. They used a narrow definition of personalized medicine restricted to pharmacogenetics as they described phenoconversion as its Achilles' heel. A more comprehensive view of personalized medicine and its application for prescribing medication, personalized prescription, considers not only genetic factors but environmental and personal factors [2]. Inhibitors, among environmental factors, and inflammation, among personal factors, can cause phenoconversion to a poor metabolizer (PM) phenotype. Personalized prescription can be implemented as personalized drug selection and personalized dosing [2]. Combining pharmacogenetics and therapeutic drug monitoring (TDM) is the best way for implementing personalized dosing [3]. Moreover, with TDM, phenoconversion is no longer a problem but a helpful piece of additional information.

Venlafaxine and risperidone TDM and CYP2D6 genotyping are described as examples. A plasma O-desmethylvenlafaxine/venlafaxine concentration ratio <1 signals the absence of CYP2D6 activity, explained by 1) genetic PM status, or 2) phenoconversion after taking a powerful CYP2D6 inhibitor, or from competitive inhibition after the use of venlafaxine itself [4]. Shah and Smith described them, respectively, as gPM and pPM [1]. Preskorn et al. [4], using this ratio, found that venlafaxine had mild CYP2D6 inhibitory properties and that 21% (159/748) of CYP2D6 extensive metabolizers (EMs) experienced phenoconversion to pPM status. Not unexpectedly, nine subjects with a genotype of CYP2D6 *4/*10 (a null allele and an allele with very low activity) had a median ratio of 1.2, since venlafaxine competitively inhibited the very limited CYP2D6 activity they had.

A risperidone TDM ratio was first used in psychiatry to detect phenoconversion during a risperidone North American randomized clinical trial (RCT) [5]. CYP2D6 EMs had higher plasma 9-hydroxyrisperidone concentrations than risperidone concentrations. If we then calculate a risperidone/9-hydroxyrisperidone ratio for CYP2D6 EMs, the ratio is <1 [6]. An inverted ratio, with higher concentrations of risperidone than 9-hydroxyrisperidone, occurred in CYP2D6 PMs and was expected in 50% of CYP2D6 EMs taking paroxetine or fluoxetine [5]. Unfortunately, the RCT risperidone TDM data

was never published by the company in a peer-review journal but was only presented in a poster. In a review article [7], graphics summarized the TDM data from the RCT by focusing on the mean values of the risperidone/9-hydroxyrisperidone ratio and the total concentration-to-dose ratio (C/D ratio), a measure of risperidone clearance from the body. The total concentration is calculated by adding the risperidone and 9-hydroxyrisperidone plasma concentrations [7].

In a naturalistic study of risperidone pharmacogenetics, 277 patients provided risperidone TDM data [8]. Table 1 shows that an inverted ratio (risperidone/9-hydoxirisperidone ratio >1) was present in almost every CYP2D6 gPM, 95% (19/20) versus 15% (39/257) for the rest of the patients. Phenoconversion was particularly frequent, 83% (5/6), in the intermediate metabolizers [IMs] taking CYP2D6 inhibitors.

A clobazam TDM ratio may also be used to establish phenoconversion. After reviewing the clobazam literature, we have proposed that a steady-state plasma N-desmethylclobazam/clobazam ratio >25 will identify a CYP2C19 gPM as long as CYP2C19 inhibitors are absent [9]. Interpreting clozapine TDM is more complex, requiring stratification by smoking and gender because they influence CYP1A2 activity. A clozapine concentration/dose ratio of >1.20 in a US female non-smoker is suggestive of poor clozapine metabolism [10].

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Table 1. Frequency of inverted ratios in risperidone TDM study with 277 patients

	Frequency of inverted ratios[1]		
	Total sample	On inhibitors[2]	No inhibitors
CYP2D6 genotyping[3]			
gPMs	95% (19/20)		
Non gPMs	15% (39/257)[4]	63% (27/43)[4]	6% (12/214)[4]
gIMs	43% (13/30)[4]	83% (5/6)[4]	33% (8/24)[4]
gEMs	12% (26/219)[4]	61% (22/36)[4,5]	2% (4/183)[4]
gUMs	0% (0/8)	0% (0/1)	0% (0/7)

[1]Another factor influencing an inverted ratio was body weight. After excluding the CYP2D6 gPMs, a logistic regression analysis of R/9-OHR >1 was performed. The significant variables were the number of CYP2D6 active alleles (odds ratio OR=0.18, 99% confidence interval, 0.08, 0.43), use of CYP inhibitors (OR=16.7; 6.2, 44.9), and body weight higher than the sample mean (OR=0.27, 0.10, 0.69).

[2]Bupropion, fluoxetine or paroxetine. Bupropion is a moderate CYP2D6 inhibitor; paroxetine and fluoxetine are potent CYP2D6 inhibitors.

[3]g refers to genetic. This is the terminology proposed by Shah and Smith [1].

[4]Any patient who is not a gPM and has an inverted ratio would be a pPM according to the terminology proposed by Shah and Smith [1].

[5]Phenoconversion is influenced by CYP2D6 genotype. In the 36 gEMs on inhibitors, the frequency of inverted ratios was 61%, but the prevalence varied according to the number of active alleles: 80% (12/15) in those with 1.0 active allele, 71% (5/7) in those with 1.4 active alleles, and 36% (5/14) in those with 2.0 active alleles.